Amendments to the specification:

Please delete paragraphs: 266, 285-287, 437, and 438

At paragraph 7, please replace the original paragraph with the following paragraph:

[7.] Acute Myelogenous Leukemia (AML) is a heterogeneous group of neoplasms with a progenitor cell that, under normal conditions, gives rise to terminally differentiated cells of the myeloid series (erythrocytes, granulocytes, monocytes, and platelets). As in other forms of neoplasia, AML is associated with acquired genetic alterations that result in replacement of normally differentiated myeloid cells with relatively undifferentiated blasts, exhibiting one or more type of early myeloid differentiation. AML generally evolves in the bone marrow and, to a lesser degree, in the secondary hematopoietic organs. AML primarily affects adults, peaking in incidence between the ages of 15-40 ~~years~~, but it is also known to affect both children and older adults. Nearly all patients with AML require treatment immediately after diagnosis to achieve clinical remission, in which there is no evidence of abnormal levels of circulating undifferentiated blast cells.

At paragraph 9 please replace the original paragraph with the following paragraph:

[9.] Several other humanized and chimeric antibodies are under development or are in clinical trials. In addition, a humanized Ig that specifically reacts with CD33 antigen, expressed both on normal myeloid cells as well as on most types of myeloid leukemic cells, was conjugated to the anti-cancer drug calicheamicin, CMA-676 (Sievers *et al., Blood Supplement,* 308, 504a (1997)). This conjugate, known as the drug MYLOTARG® ~~Mylotarg®~~, has recently received FDA approval (Caron *et al., Cancer Supplement,* 73, 1049-1056 (1994)). In light of its cytolytic activity, an additional anti-CD33 antibody (HumM195), currently in clinical trials, was conjugated to several cytotoxic agents, including the gelonin toxin (McGraw et al., *Cancer Immunol. Immunother,* 39, 367-374 (1994)) and radioisotopes ^{131}I (Caron et al., *Blood* 83, 1760-1768 (1994)), ^{90}Y (Jurcic et al., *Blood Supplement,* 92, 613a (1998)) and ^{213}Bi (Humm et al., *Blood Supplement,* 38:231P (1997)).

At paragraph 20 please replace the original paragraph with the following paragraph:

[20.] The N-terminal globular domain of GPIbα contains a cluster of negatively charged amino acids. Several lines of evidence indicate that, in transfected CHO cells expressing GPIb-IX complex and in platelet GPIbα, the three tyrosine residues contained in this domain (Tyr-276, Tyr-278, and Tyr-279) undergo sulfation.

At paragraph 29 please replace the original paragraph with the following paragraph:

[29.] A commercially available monoclonal antibody to human PGSL-1, KPL1, was generated and shown to inhibit the interactions between PGSL-1 and P-selectin and between PGSL-1 and L-selectin. The KPL1 epitope was mapped to the tyrosine sulfation consensus motif of PGSL-1 (YEYLDYD) (SEQ ID NO: 214) (Snapp et al., Blood 91 1:154-164 (1998)). KPL1 recognizes only this particular epitope and does not cross-react with sulfated epitopes present on other cells, such as B-CLL cells, AML cells, metastatic cells, multiple myeloma cells, and the like.

At paragraph 36 please replace the original paragraph with the following paragraph:

[36] There are two forms of normal human fibrinogen: fibrinogen γ major and fibrinogen γ prime minor variant, each of which is found in normal individuals. Normal fibrinogen, which is the more abundant form (comprising ~90% of the fibrinogen found in the body), is composed of two identical 55 kDa alpha (α) chains, two identical 95 kDa beta (β) chains, and two identical 49.5 kDa gamma (γ) chains. Normal variant fibrinogen, which is the less abundant form (comprising ~10% of the fibrinogen found in the body), is composed of two identical 55 kDa alpha (α) chains, two identical 95 kDa beta (β) chains, one 49.5 kDa gamma (γ) chain, and one 50.5 kDa gamma prime (γ') chain. The gamma and gamma prime chains are both coded for by the same gene, with alternative splicing occurring at the 3' end. Normal gamma chain is composed of amino acids 1-411. Normal variant gamma prime chain is composed of 427 amino acids: amino acids 1-407 are the same as those in the normal gamma chain, and amino acids 408-427 are VRPEHPAETEYDSLYPEDDL (SEQ ID NO: 220). This region is normally occupied with thrombin molecules.

At paragraph 55 please replace the original paragraph with the following paragraph:

[55] Also provided by the present invention is an antibody multimer comprising at least a first and second antigen binding fragment, wherein the at least first or second antigen binding fragment or both is capable of binding or cross-reacting with an epitope comprising the formula (SEQ ID NO:216):

$$(G)_z(X)_u(E)_n(D)_m(Y)_t(X)_u(E)_n(D)_m(Y)_t(X)_u(E)_n(D)_m(Y)_t(D)_m(E)_n(X)_u$$

with $(S)_r$ attached to each $(Y)_t$ Formula III

Wherein:

G is Glycine

E is Glutamate

D is Aspartate

Y is Tyrosine

S is sulfate or a sulfated molecule

X is any amino acid except the above

z is 0, 1, or 2

t is 1, 2 or 3

r is 0 or 1

u is 0 to 2

n is 0 to 3

m is 0 to 3

wherein at least one Y is sulfated; wherein if n = 0 then m > 0; wherein if m = 0 then n > 0.

At paragraph 64 please replace the original paragraph with the following paragraph:

[64.] In a preferred embodiment the pharmaceutical composition of the invention comprises agent selected from an anti-viral agent selected from the group consisting of acyclovir, ganciclovir and zidovudine. In other embodiments the pharmaceutical composition comprises an agent selected from anti-thrombosis/ anti- restenosis agents selected from the group consisting of cilostazol, dalteparin sodium, reviparin sodium, and aspirin; or the pharmaceutical composition comprises an anti-inflammatory agent selected from the group consisting of zaltoprofen, pranoprofen, droxicam, acetyl salicylic 17, diclofenac, ibuprofen, dexibuprofen, sulindac, naproxen, amtolmetin, celecoxib, indomethacin, rofecoxib, and nimesulid; or an anti- autoimmune agent selected from the group consisting of leflunomide, denileukin diftitox, subreum, WinRho SDF, defibrotide, and cyclophosphamide; or an anti- adhesion/anti-aggregation agent selected from the group consisiting of limaprost, clorcromene, and hyaluronic acid; or a pharmaceutical agent selected from the group consisting of doxorubicin (adriamycin), morpholinodoxorubicin, methoxymorpholinyldoxorubicin ~~(morpholinodoxorubicin), adriamycin~~, cis-platinum, taxol, calicheamicin, vincristine, cytarabine (Ara-C), cyclophosphamide, prednisone, daunorubicin, morpholinodaunorubicin, methoxymorpholinyldaunorubicin, idarubicin, ludarabine, chlorambucil, interferon alpha, hydroxyurea, temozolomide, thalidomide and bleomycin, and derivatives and combinations thereof. In another embodiment of the invention the pharmaceutical agent is coupled to or complexed with a vehicle or carrier that is capable of being coupled or complexed to more than one agent. In a preferred embodiment the vehicle or carrier is selected from the group consisting of dextan, lipophilic polymers, ~~lipophiolic polymers~~, hydrophilic polymers, HPMA and liposomes.

At paragraph 67 please replace the original paragraph with the following paragraph:

[67.] Antibodies (Ab's), or immunoglobulins (Ig[[G]]'s), are protein molecules that

bind to antigen. They are composed of units of four polypeptide chains (2 heavy and 2 light) linked together by disulfide bonds. Each of the chains has a constant and variable region. They can be divided into five classes, IgG, IgM. IgA, IgD, and IgE, based on their heavy chain component. The IgG class encompasses several sub-classes including, but not restricted to, IgG_1, IgG_2, IgG_3, and IgG_4. Immunoglobulins are produced *in vivo* by B lymphocytes and recognize a particular foreign antigenic determinant and facilitate clearing of that antigen.

At paragraph 85 please replace the original paragraph with the following paragraph:

[85.] Conservative amino acid substitution is defined as a change in the amino acid composition by way of changing one or two amino acids of a peptide, polypeptide or protein, or fragment thereof. The substitution is of amino acids with generally similar properties (e.g., acidic, basic, aromatic, size, positively or negatively charged, polar, non-polar) such that the substitutions do not substantially in a major way alter peptide, polypeptide or protein characteristics (e.g., charge, <u>isoelectric point</u> [[IEF]], affinity, avidity, conformation, solubility) or activity. Typical substitutions that may be performed for such conservative amino acid substitution may be among the groups of amino acids as follows:

(i) glycine (G), alanine (A), valine (V), leucine (L) and isoleucine (I)

(ii) aspartic acid (D) and glutamic acid (E)

(iii) alanine (A), serine (S) and threonine (T)

(iv) histidine (H), lysine (K) and arginine (R)

(v) asparagine (N) and glutamine (Q)

(vi) phenylalanine (F), tyrosine (Y) and tryptophan (W)

At paragraph 87 please replace the original paragraph with the following paragraph:

[87.] A phagemid is defined as a phage particle that carries plasmid DNA. Phagemids are plasmid vectors designed to contain an origin of replication from a filamentous phage, such as <u>M13</u> [[m13]] <u>or</u> [[of]] fd. Because it carries plasmid DNA, the phagemid particle does not have sufficient space to contain the full complement of the phage

genome. The component that is missing from the phage genome is information essential for packaging the phage particle. In order to propagate the phage, therefore, it is necessary to culture the desired phage particles together with a helper phage strain that complements the missing packaging information.

At paragraph 92 please replace the original paragraph with the following paragraph:

[92.] An anti-leukemia agent is an agent with anti-leukemia activity. For example, anti-leukemia agents include agents that inhibit or halt the growth of leukemic or immature pre-leukemic cells, agents that kill leukemic or pre-leukemic cells, agents that increase the susceptibility of leukemic or pre-leukemic cells to other anti-leukemia agents, and agents that inhibit metastasis of leukemic cells. In the present invention, an anti-leukemia agent may also be agent with anti-angiogenic activity that prevents, inhibits, retards or halts vascularization of tumors.

At paragraph 98 please replace the original paragraph with the following paragraph:

[98.] FIG. 3 is an outline of Y1 reactivity with different preparations of platelet GC and membrane fraction 4 of KG-1 cells ~~the optimal determinants for binding of Y1 to its epitope~~.

At paragraph 119 please replace the original paragraph with the following paragraph:

[119.] FIG. 24 depicts the immunoprecipitation scheme used in the analysis of the specificity of Y1 ~~binding ,the results of which are depicted in FIG. Tab 2A, page 17B~~.

At paragraph 127 please replace the original paragraph with the following paragraph:

[127.] FIG. 33 depicts a Western Blot showing the effect of Aryl-Sulfatase and Mocarhagin cleavage on Y1 binding. ~~FIG. 33 is a graph depicting liver weights (mean +/- SEM) of mice at day 35.~~

At paragraph 133 please replace the original paragraph with the following paragraph:

[133.] FIG. 39 is a graph illustrating the pharmacokinetics ~~pharmakokinetics~~ of

TCA-precipitable radioactivity in plasma after intravenous injection of ^{125}I-CONY1 in mice. The sequence of CONY1 is presented at SEQ ID NO: 204.

At paragraph 144 please replace the original paragraph with the following paragraph:

[144] FIG. 50 provides the amino acid and nucleotide sequences of the Y16 scFv (SEQ ID NOS: 210 & 213).

At paragraph 151 please replace the original paragraph with the following paragraph:

[151.] Proteins extracted from human platelets were Western blot analyzed on SDS-PAGE using the Y1 scFv antibody and the Y17 scFv antibody, in order to identify the epitopes ~~receptors~~ to which the antibodies bind on the surface of the platelets. Using this methodology, it was determined that the Y1 scFv and Y17 scFv epitope on platelets is glycocalicin, one of the subunits of the CD42 complex.

At paragraph 163 please replace the original paragraph with the following paragraph:

[163] A preferred epitope is the epitope of Formula II wherein: W is Glycine; Y is a peptide conjugate of Tyrosine or a glyco conjugate of Asparagine, Serine or Threonine; A is Glutamate, γ Carboxy Glutamate or Aspartate, Leucine, Isoleucine Phenylalanine, Serine or Glycine. In certain embodiments, Y is a peptido conjugate of Tyrosine; q is 3; and r is 1.

Formula (III) (SEQ ID NO: 216):

$$(G)_z(X)_u(E)_n(D)_m(Y)_t(S)_r\,(X)_u(E)_n(D)_m(Y)_t(S)_r(X)_u(E)_n(D)_m(Y)_t(S)_r(D)_m(E)_n(X)_u$$

Wherein:

G is Glycine

E is Glutamate

D is Aspartate

Y	is Tyrosine
S	is sulfate or a sulfated molecule
X	is any amino acid except the above
z	is 0, 1, or 2
t	is 1, 2 or 3
r	is 0 or 1
u	is 0 to 2
n	is 0 to 3
m	is 0 to 3

wherein at least one Y is sulfated; wherein if n = 0 then m > 0; wherein if m = 0 then n > 0; and further wherein the isolated epitope is capable of being bound by an antibody, antigen-binding fragment thereof, or complex thereof comprising an antibody or binding fragment thereof, comprising a first hypervariable region comprising SEQ ID NO: 8 or SEQ ID NO: 20.

At paragraph 166 please replace the original paragraph with the following paragraph:

[166] Such epitopes are found on such diverse molecules as GPIb and PSGL-1 and are found on certain diseased cells, such as B-CLL cells, AML cells, multiple myeloma cells, and metastatic cells. Sulfation of tyrosine and/ or other moieties is particularly important for binding to these epitopes. Human proteins known to be tyrosine sulfated include the following:

Peptide	**Sequence**
Thrombomodulin (408-426)	E C P E G Y I L D D G F I C T D I D E (SEQ ID NO: 217)
Human GPIbα (269-287)	D E G D T D L Y D Y Y P E E D T E G D (SEQ ID NO: 218)

Human Heparin Cofactor II (56-75)	G E E D D D Y L D L E E D D D Y I D I V D (SEQ ID NO: 219)
Human Fibrinogen γ' (408-427)	V R P E H P A E T E Y D S L Y P E D [[O]] D L (SEQ ID NO: 220)
α-2-Antiplasmin	P P M E E D Y P Q F G S P (SEQ ID NO: 221)
Cholecystokinin (CCK)	R I S D R D Y M G W M D F (SEQ ID NO: 222)
α-2-Choriogonadotropin	C H C S T C Y Y H K S – C O O H (SEQ ID NO: 223)
Complement C4	M E A N E D Y E D Y E Y D E L P A K (SEQ ID NO: 224)
PSGL-1	Q A T E Y E Y L D Y D F L P E T E (SEQ ID NO: 225)
Factor VIII (716-731)	G D Y Y E D S Y E D I S A Y L L (SEQ ID NO: 226)
Lumican	YYDYDFPL (SEQ ID NO: 227)

At paragraph 172 please replace the original paragraph with the following paragraph:

[172.] A second scFv clone, Y17, which binds to platelets and cell lines derived from human myleogenous leukemia cells, particularly AML cells, was also selected. Y17 scFv has the sequence SEQ ID NO: 203. The binding characteristics of Y17 are primarily attributable to its heavy chain CDR3 region, which has the sequence SEQ ID NO: 20. ~~Full Y17 IgG antibodies were also produced.~~

At paragraph 175 please replace the original paragraph with the following paragraph:

[175.] The hypervariable regions of antibodies of the invention form the antigen binding sites of antibodies of the present invention. The antigen-binding site is complementary to the structure of the epitopes to which the antibodies bind and therefore are referred to as complementarity-determining regions (CDRs). There are three CDRs on each light and heavy chain of an antibody, each located on the loops that connect the β strands of the V_H and V_L domains.[[.]]

At paragraph 193 please replace the original paragraph with the following paragraph:

[193.] The DNA fragment encoding the V_L domain (variable light chain) of human antibody was PCR-cloned from the Y1 clone (the identical DNA fragment can be obtained from any other clone in the Nissim I library (Nissim et al., "Antibody fragments from a 'single pot' phage display library as immunochemical reagents," *EMBO J.* 13(3): 692-698 (1994)) or even from the human genome using the same methodology) with the following synthetic oligonucleotide primers: oligo 5'-*Nde*1 (TTTCATATGGAGCTGACTCAGGACCCTGCT)(SEQ ID NO: 228) and oligo 3'-*Eco*RI (TTTGAATTCCTATTTTGCTTTTGCGGC)(SEQ ID NO: 229). After amplification by polymerase chain reaction (PCR conditions: 94° C for 1[[']] min., 56° C for 2 [[']] min., 72° C for 2[[']] min. x 30 then 65° C for 5[[']] min.) the obtained DNA fragment was digested with *Nde*I and *Eco*RI restriction enzymes and cloned into *Nde*I and *Eco*RI restriction enzymes sites of a pre-digested plasmid, which is an IPTG inducible expression vector used for prokaryotic expression of recombinant proteins in *E. coli*. *E. coli* cells were transformed with the ligation mixture and positive clones were selected by PCR amplification using the above oligonucleotide primers. Cells harboring this plasmid were grown and induced for expression by IPTG. Bacterial cells were harvested by centrifugation from 1 liter of culture post induction with IPTG, inclusion bodies were isolated and solubilized in guanidine-HCl + DTT ~~DTE~~, and refolded by dilution in a buffer containing Tris-Arginine-EDTA ~~TRIS-ARGININE-EDTA~~. After refolding at 5-10° for 48 hrs, the solution containing protein was dialyzed and concentrated to 20mM Glycine pH 9. The dialyzed solution containing proteins was re-purified by using an ionic exchange column, HiTrapQ, and eluted with a gradient of NaCl. The main peak was analyzed by SDS-PAGE and by gel filtration. At least 10 mgs of purified V_L were obtained from an original 1liter culture.

At paragraph 194 please replace the original paragraph with the following paragraph:

[194.] Rabbits were immunized with V_L (400mg) in the presence of CFA (complete Freund's ~~Fruend's~~ adjuvant) then by V_L (200mg) in the presence of IFA (incomplete Freund's ~~Fruend's~~ adjuvant) at 2 to 4 weeks intervals. The titers obtained were low (1:50-1:100) probably due to the high homology between the V_L's from human and rabbit.

At paragraph 196 please replace the original paragraph with the following paragraph:

[196.] Rabbits were immunized with 400 mg of 1:1 ratio mixture of the purified scFv antibody fragments in the presence of complete Freund's ~~Fruend's~~ adjuvant then with 200 mg of that mixture in the presence of incomplete Freund's ~~Fruend's~~ adjuvant, at 2 to 4 weeks intervals.

At paragraph 202 please replace the original paragraph with the following paragraph:

[202.] In order to characterize the epitope on the platelet membrane to which Y1 binds, platelet surface proteins were separated by SDS-PAGE (under both reducing and non-reducing conditions) and immunoblotted with biotin labeled-Y1. ~~under reducing and non-reducing conditions.~~ The results of this experiment demonstrate that Y1 reacts with a protein with a molecular mass of 135 kDa under reducing conditions, and with a protein with molecular mass of ~160 kDa under non-reducing conditions. These molecular masses correspond to platelet GPIbα, which has a molecular mass of 135 kDa under reducing conditions. Under non-reducing conditions, the GPIbα chain disulfide-linked to GPIb∃ has a molecular mass of 160-kDa. (FIG. 2).

At paragraph 205 please replace the original paragraph with the following paragraph:

[205.] Western analysis of recombinant GPIb expressed in *E. coli* demonstrated that GPIb expressed in *E. coli* does not react with Y1. Thus, it appears that post-translational modification, which does not occur in *E. coli* is required for Y1 binding. Neither N- nor O-glycanases affect the binding of Y1 to KG-1 cells. However, Y1 binding can be inactivated (eliminated) by treatment of ligands with aryl sulfatases or by proteases. (FIG. 3).

At paragraph 210 please replace the original paragraph with the following paragraph:

[210.] Washed platelets were treated by mocarhagin, and platelet lysates were electrophoresed on SDS-polyacrylamide gels and transferred to nitrocellulose. Western blot analysis of lysates of mocarhagin-treated washed platelets with Y1 shows a loss of the band corresponding to GPIbα (135 kDa[[ ]]) and binding of Y1 to the N-terminal ~45 kDa ~~tryptic~~

fragment. A monoclonal antibody (MCA466S) directed against the C-terminal fragment of GPIbα reacted with the ~95 kDa C-terminal fragment, and a monoclonal antibody (S.C.7071) directed against the N-terminal fragment of GPIbα reacted with the same ~45 kDa fragment that was recognized by Y1. (FIG. 7).

At paragraph 220 please replace the original paragraph with the following paragraph:

[220.] ELISA assays were developed to evaluate the effect of the GPIb derived synthetic peptides on the binding of Y1 to purified glycocalicin. In addition, FACS analysis using washed platelets was carried out. To evaluate the importance of sulfated tyrosine within the Y1 binding site of GPIb, a competitive binding FACS analysis was used. Y1-scFv at a concentration of 1 μg was preincubated with different peptides at concentrations of 2.5 and 200 μM. After a preincubation for 30 minutes at room temperature the mixture was added to a tube containing ~10^7 washed platelets and the binding of Y1 to the washed platelets was assessed using polyclonal rabbit anti-scFv-PE. The inhibitory effect of the peptides compared to control binding (Y1 alone) was evaluated by measuring the residual binding of Y1 to washed platelets. The peptides and the results are described in Tables 1 and 3, respectively ~~Table 1~~, and are similar to results that were observed using the same peptides in an ELISA assay (Table 2) ~~(Table B)~~. In both assays, a control level of Y1 binding was determined, as follows. A polystyrene microtiter MaxiSorp ~~maxisorb~~ plate was coated with (a) purified glycocalicin or (b) washed platelets. After extensive washing, 0.5 μg/well of Y1 was added. The plate was then incubated with rabbit anti-scFv followed by addition of anti rabbit –HRP (horse radish peroxidase) and HRP substrate. The level of anti rabbit -HRP binding was measured by the intensity of the color produced, and the level of anti rabbit - HRP binding correlates with the level of binding of anti Y1-scFv and the level of binding of Y1. The optical density was measured at A_{405}. Each sample was assayed in duplicate, and the average was calculated.

At paragraph 222 please replace the original paragraph with the following paragraph:

[222] The five peptides are as follows in Table 1:

Table 1

Peptide Name	Characterization	Sequence
EGR	negative control peptide	REEGRQHFFLLEGRSSYS (SEQ ID NO: 230)
P-1	residues 268-285 of GPIbα	GDEGDTDLYDYYPEEDTE (SEQ ID NO: 231)
P- 1-S	residues 268-285 of GPIbα	GDEGDTDLY*DY*Y*PEEDTE (SEQ ID NO: 232)
P-2-S	residues 273-285 of GPIbα	TDLY*DY*Y*PEEDTE (SEQ ID NO: 233)
P-3-S	residues 268-280 of GPIbα	GDEGDTDLY*DY*Y*P (SEQ ID NO: 234)

Y* is identical to Y which is sulfated tyrosine.

At paragraph 225 please replace the original paragraph with the following paragraph:

[225.] These results further support the hypothesis that sulfated tyrosine residues within the specific region are important for Y1 recognition on GPIb. Overall, analysis of N-terminal peptide proteolytic fragments of mocarhagin and cathepsin G suggest that the GPIbα amino acid sequence Tyr –276[[-]] to Glu-282 is or contains an important epitope for binding of Y1. (FIG. 3) [[(FIGS. Tab 1C pages 6 and 7)]]. Further characterization indicated that in addition to residues 276-282 (sulfated anionic sequence) of glycocalicin, upstream amino acids 283-285 are involved in the recognition site of Y 1.

Biological Activity Of Y1 scFv , Y17 scFv and IgG Y1 On Platelets Function

At paragraph 229 please replace the original paragraph with the following paragraph:

[229.] The effect of Y1 (scFv) on aggregation of platelet-rich-plasma (PRP) was tested at various concentrations of Y1. PRP was pre-incubated with Y1 scFv, Y17 scFv, or a

control TM-1 scFv ~~sTM-1cFv~~ for 4 min at 37°C before being exposed to ristocetin, an inducer of platelet agglutination and aggregation. A reversible inhibitory effect was observed when scFv was added to PRP prior to the addition of ristocetin, and it was dose dependent.

At paragraph 232 please replace the original paragraph with the following paragraph:

[232.] Due to its natural structure the full IgG Y1 has two binding sites for [[on]] GPIbα and one binding site for an Fc receptor. It is likely that if full IgG Y1 binds two GPIbα molecules, it will activate platelets and induce platelet agglutination. Furthermore, because platelets have a ~~n~~ Fc-receptor, Y1-IgG can induce platelet agglutination by binding to GPIbα and to a ~~n~~ Fc-receptor, thereby producing platelet agglutination by each IgG Y1 binding to three platelets. Therefore, the effect of IgG Y1 on aggregation of washed platelets was tested at different concentrations of Y1-IgG in the presence or absence of ristocetin. Induction of platelet aggregation by Y1-IgG was monitored for 4 min at 37°C, followed by addition of ristocetin.

At paragraph 236 please replace the original paragraph with the following paragraph:

[236.] The results are presented in Table 7 and FIG. 18. No effect on platelet aggregation was seen after the addition of ristocetin: normal platelet aggregation was observed. Y1-IgG at a final concentration of 50 μg/ml induced platelet aggregation in Platelet-Rich-Plasma, before the addition of ristocetin. Y1-IgG at a concentration of 25 μg/ml only partially induced platelet aggregation before the addition of ristocetin. No inhibition ~~induction~~ of platelet aggregation was observed with Y1-IgG concentrations of 10 μg/ml, 4 μg/ml, or 1 μg/ml. Commercial monoclonal antibodies against GPIbα (Pharmigen), which inhibit platelet aggregation at concentration of 20 μg/ml, did not induce platelet aggregation. Control human IgG- Lambda (Sigma) in the same concentration as Y1-IgG also did not induce platelet aggregation.

At paragraph 237 please replace the original paragraph with the following paragraph:

[237.] Antibodies against GPIbα (CD42b) recognize platelet lysate and glycocalicin

[and] but not KG-1 cell lysate (a Y1 binding positive myeloid cell line) or RAJI ~~Raji~~ cell lysate (a B cell line that is negative for Y1 binding at concentrations at which KG-1 cells are positive for Y1 binding). In contrast, Y1 recognized both glycocalicin, platelet lysate, and KG-1 cells, but not RAJI ~~Raji~~ cell extract. The negative control scFv-181, did not recognize any of the relevant proteins. (FIG. 20).

At paragraph 239 please replace the original paragraph with the following paragraph:

[239] Two proteins immunoreacted with Y1 both in normal as well as in leukemia patients plasma. The first is designated H P-ligand 1, which has a molecular mass of ~50 kDa under reducing conditions and >300 kDa under non-reducing conditions and which completely disappears from the serum after coagulation; and (2) H P-ligand 2, which has a molecular mass of ~80 kDa under both reducing and non-reducing conditions and which remains in serum after coagulation. After purification using a Q-Sepharose column reverse phase (RP-HPLC) 2D gel electrophoresis, and peptide mapping, the ~50 kDa ligand was identified as the normal variant of the gamma·chain (γ prime) of human fibrinogen. The sequence VRPEHPAETEYDSLYPEDDL (SEQ ID NO: 220), is present only in fibrinogen gamma prime, but not the abundant form of fibrinogen gamma, and is similar to GPIb anionic region containing sulfated tyrosine. Most likely this is the binding site for Y1. The ~80 kDa was identified as complement compound 4 (CC4) and Lumican. As above, it contains sulfated tyrosine residues accompanied by a stretch of negatively charged amino acids.

Binding of Y1 to Primary Leukemia Cells

At paragraph 240 please replace the original paragraph with the following paragraph:

[240.] FACS analysis indicated that Y1 and Y17 have similar binding profiles to platelets and KG-1. In addition, both do not bind to RAJI ~~Raji~~ and T2 cells. In contrast, TM1 (SEQ ID NO: 209), Y16 (SEQ ID NO: 210) and Y45 do not bind to any of the above mentioned human cell lines.

At paragraph 243 please replace the original paragraph with the following paragraph:

[243.] The table below summarizes the biochemical experiments preformed to characterize and localize the Y1 binding site on KG-1 cells.

Western Blot Analysis with Y1 on SDS-PAGE Reducing Gels

Table 10

Substrate	Treatment	Condition	Reactivity with Y1	Presented in Figure
RP-HPLC KG-1 membrane fraction	O-Sialo glycoprotein endopeptidase	30' at 37^{0}C	Reactivity only with the 120kDa form	FIG. 22 ~~Tab 2A slide 14~~
RP-HPLC KG-1 membrane fraction	O-Sialo glycoprotein endopeptidase	4hr at 37^{0}C	No reactivity	FIG. 22 ~~Tab 2A slide 14~~
RP-HPLC KG-1 membrane fraction	aryl-sulfatase	18hr at 22^{0}C	No reactivity	FIG. 23 ~~Tab 2A slide 14~~
RP-HPLC KG-1 membrane fraction	Mocarhagin	7' at 37^{0}C	No reactivity	FIG. 33 ~~Tab 2A slide 14~~
Glycocalicin (GC)	O-Sialo glycoprotein endopeptidase	30' at 37^{0}C	Enhanced binding	FIG. 22 ~~Tab 2A slide 14~~
Heparin – BSA	aryl-sulfatase	18hr at 22^{0}C	Binds to Y1 as without treatment	FIG. 23 ~~Tab 2A slide 16~~

At paragraph 244 please replace the original paragraph with the following paragraph:

[244.] In summary, following treatment with endopeptidases the Y1 signal is cleaved off and cannot be detected (FIG. 22). Most likely, the fragment containing the Y1 binding site is found on the N-terminus ~~N' terminus~~ and it is too small to be detected [determined] under the conditions used in the above experiments. Likewise, following treatment with Mocarhagin, the Y1 signal is cleaved off and cannot be detected (FIG. 33), suggesting that the epitope for Y1 is found on the N' terminus of the ligand. In addition, the results obtained with the aryl-sulfatase which remove sulfate entities from proteins (within the KG-1 cell extract), but not from sugar moieties (on the heparin) further support our hypothesis that sulfate is required for Y1 recognition (FIG. 23). Interestingly, O-Sialo glycoprotein endopeptidase enhanced the Y1 signal in the GC cleavage product. We assume that following this treatment the Y1 binding site, now located at the C-terminus ~~C' terminus~~ is better

exposed to the Y1 binding.

Correlation between Y1 and PSGL-1 antibody-KPL1: Western Blot Analysis

At paragraph 250 please replace the original paragraph with the following paragraph:

[250.] Analysis of binding of scFv Y1 antibodies and anti-CD162 antibodies to diseased cells also illustrates that scFv Y1 has binding characteristics different from those of anti-CD162 antibodies. Specifically, FACS analysis of Y1 and anti-CD162 binding to Pre-B-ALL, HCL, AML, B-ALL, B-CLL, unclassified leukemia, B-PLL, and multiple myeloma cells from human patients showed the two antibodies have different binding profiles. (Table 11) ~~(Table F)~~. Y1 binds to the leukemic cells in 10 of 12 samples. In contrast, anti-CD162 bound only 5 out of 12 samples. Out of the 12 samples, 5 were found to bind Y1 but not anti-CD162. Thus, it may be concluded that, in leukemic cells, scFv Y1 binds to a ligand other than that recognized by anti-CD162.

Table 11: Leukemia samples -- Analysis of Anti-CD162 versus Y1

		Reaction with the Leukemia Cells	
Patient #	**Disease**	ScFv Y1	**Anti CD162**
42291	Pre-B-ALL	+	-
42299	HCL	-	-
42311	AML	+	+
42321	B-ALL	-	-
42323	B-CLL	+	-
42325	Unclassified	+	-
42332	B-CLL	+	-
42352	B-PLL	+	+/-
42330	AML	+	+
42334	MM	+	-
42366	AML	+	+
42370	AML/ALL	+	+/-

At paragraph 251 please replace the original paragraph with the following paragraph:

[251.] Overall, sulfated-tyrosine containing Y1-binding domains in GPIbα, fibronectin-γ' ~~Fng-γ prime~~, and PSGL-1, are DEGDTDLYDYYPEEDTEGD (amino acids

269-287)(SEQ ID NO: 218), EHPAETEYDSLYPED (amino acids [[411-427]] 412-426)(SEQ ID NO:235), and QATEYEYLDYDFLPETE (amino acids 1-17)(SEQ ID NO: 225), respectively. An additional binding site, with a higher affinity to Y1, is most likely to be expressed on primary leukemia cells. Interestingly, blood samples that are positive both to scFv Y1 and anti-CD162 were derived from AML patients, while B-cell were negative to anti-CD162.

At paragraph 255 please replace the original paragraph with the following paragraph:

[255] Thus, it is clear that not every sulfated peptide binds to scFv Y1 to the same extent. Also, significantly, these results demonstrate that only one sulfated tyrosine is necessary for binding, as can be seen with peptides P- Y*YY and P-YY Y*. Further, it can be seen that the amino acid context of the sulfated tyrosines influences Y1 binding. For example, P- Y*YY (containing one sulfated tyrosine in the sequence EY*E) inhibits binding efficiently only at 100 μM. In contrast, P-YYY*(containing one sulfated tyrosine in the sequence DY*D) inhibits binding efficiently at 1 μM.

Table 12: Sulfated Peptides

Name	Source of Peptide	Sequence	#aa	MW	Sulfation
F-YY	Fibrinogen-γ-prime chain	VRPEHPAETEYESLYPEDDL (SEQ ID NO: 236)	20	2389	-
F- Y* Y*	Fibrinogen-γ-prime chain	VRPEHPAETEY*ESLY*PEDDL (SEQ ID NO: 237)	20	2549	Sulfated
P-YYY	PSGL-1-n-terminus	QATEYEYLDYDFLPETE (SEQ ID NO: 225)	17	2126	-
P- Y*YY	PSGL-1-n-terminus	QATEY*EYLDYDFLPETE (SEQ ID NO: 238)	17	2206	Sulfated
P- Y* Y*Y	PSGL-1-n-terminus	QATEY*EY*LDYDFLPETE (SEQ ID NO: 239)	17	2286	Sulfated
P- Y*Y Y*	PSGL-1-n-terminus	QATEY*EYLDY*DFLPETE (SEQ ID NO: 240)	17	2286	Sulfated
P-Y Y*Y	PSGL-1-n-terminus	QATEYEY*LDYDFLPETE (SEQ ID NO: 241)	17	2286	Sulfated
P-Y Y* Y*	PSGL-1-n-terminus	QATEYEY*LDY*DFLPETE (SEQ ID NO: 242)	17	2286	Sulfated
P-YY Y*	PSGL-1-n-terminus	QATEYEYLDY*DFLPETE (SEQ ID NO: 243)	17	2286	Sulfated
G-YYY	GPIbα	GDEGDTDLYDYYPEEDTE (SEQ ID NO: 231)	18	2126	-
G-Y*Y*Y*	GPIb∀	GDEGDTDLY*DY*Y*PEEDTE	18	2366	Sulfated

Name	Source of Peptide	Sequence	#aa	MW	Sulfation
		(SEQ ID NO: 244)			

Y*=Sulfated Tyrosine

At paragraph 256 please replace the original paragraph with the following paragraph:

[256.] (1) Y1 resembles L-selectin which recognizes both sulfated protein and sugar moieties, and is distinct from the P-selectin [[ ]]which recognizes only sulfated proteins. Therefore, it can compete for the binding ~~bonding~~ of both proteins

At paragraph 258 please replace the original paragraph with the following paragraph:

[258.] Two human leukemia models were developed in immuno-deficient mice as well as ~~in~~ assay systems.

At paragraph 261 please replace the original paragraph with the following paragraph:

[261.] In one experiment, SCID mice were pretreated with 100 mg/kg Cytoxen (CTX, Cyclosphosphamide for injection, Mead Johnson), and were i.v. injected with $2x10^7$ MOLT-4 cells/mouse, 5 days post treatment with cyclophosphamide. Anti-cancer agents or PBS (negative control animals) were injected i.v. three times/week from day 5 post MOLT-4 cells injection and onward. On day 35, blood was drawn from the animals, the animals were sacrificed, and their livers were excised and weighed. In the untreated, PBS-treated MOLT-4 cell-bearing animals, the liver presented with a very massive tumor growth, and its size was increased 2-3-fold relative to PBS control uninfected animals. ~~In one experiment, SCID mice were pretreated with 100mg/kg Cytoxan (CTX, Cyclophosphamid for injection, Mead Johnson). Eleven days after CTX injection, MOLT-4 cells were injected intravenously into the tail vein. Control mice were injected with PBS alone. One week post MOLT-4 injection mice were injected with CONY1-Doxorubicin, which is a conjugate between scFv CON Y1 polypeptide, having KAK amino acid residues at its carboxy end and doxorubicin via a short organic linker; CONY1, which is a scFv antibody fragment derived from Y1 scFv in which the DNA sequences encoding the myc tag of Y1 were deleted and replaced with a DNA sequence encoding the amino acids lysine, alanine, lysine (KAK); or free Doxorubicin . The mice were injected three times per week for three weeks. Control mice were injected with~~

~~PBS; and another control group did not receive any treatment. (Table M).~~

In this experiment, there were five treatment groups:

1. Not injected with MOLT-4 cells, PBS treated
2. MOLT-4 injected control, PBS-treated
3. MOLT-4 injected, treated with Y1 scFv (CONY 1), 75 µg/mouse
4. MOLT-4 injected, treated with CONY 1 scFv - Doxorubicin, 75 µg/mouse
5. MOLT-4 injected, treated with Doxorubicin, 0.1 mg/kg.

Table 13

Number of Mice	Inoculation	Treatment
5	PBS only	--
9	MOLT-4	--
9	MOLT-4	CONY-Dox (2.5 mg/kg)
9	MOLT-4	CONY-Dox (2.5 mg/kg)
8	MOLT-4	Free Dox (0.1 mg/kg)

At paragraph 263 please replace the original paragraph with the following paragraph:

[263.] The results are depicted in (FIGS. 30, 31 and 32). Massive tumor growths (white nodules) were seen in the livers of all mice injected with MOLT-4 cells. [[However, livers of mice injected with MOLT-4 and treated with CONY1 or CONY1-Doxorubicin conjugate weighted significantly less than those of mice injected with MOLT-4 and treated with free Doxorubine or left untreated (FIG. 30).]]

At paragraph 268 please replace the original paragraph with the following paragraph:

[268.] The liver weights, on day 35, are presented in (FIG. 30) ~~(FIG. 33)~~. As shown, liver size almost tripled in the tumor-infected mice, negative control PBS treated relative to PBS control, and non-MOLT-4-injected mice. The liver weights of mice treated with a low dose of Doxorubicin were similar to that of PBS treated tumor-infected mice. On the other hand, CONY1 scFv and CONY1 scFv-Doxorubicin conjugate treatments markedly inhibited

tumor growth in the liver (much lower liver weights).

At paragraph 269 please replace the original paragraph with the following paragraph:

[269.] In a second ~~In a third~~ experiment, using the identical SCID/MOLT-4 protocol, there were 6 groups:

1. Not injected with MOLT-4, PBS control ~~PBS control, uninfected MOLT-4 cells~~
2. MOLT-4 injected, treated with PBS ~~PBS treated Molt control~~
3. MOLT-4 ~~Molt~~ injected ~~group~~, treated with CONY1 scFv, 75 μg/mouse
4. MOLT-4 ~~Molt~~ injected ~~group~~, treated with a non-specific scFv antibody derived from the Nissim I library, 75 μg/mouse (control)
5. MOLT-4 Molt injected ~~group~~, treated with Y1-IgG, 5 μg/mouse. ~~6. MOLT-4 group, treated with a non-specific human IgG, 5 μg/mouse (control)~~
6. MOLT-4 group, treated with a non-specific human-IgG, 5μg/mouse (control)

At paragraph 273 please replace the original paragraph with the following paragraph:

[273.] In a first experiment, NOD/SCID mice were pretreated with 100mg/kg CYTOXAN® ~~CYTOXAN®~~. Four days post CYTOXAN® ~~CYTOXAN®~~ injection, KG-1 cells were injected intravenously into the tail vein of six groups of mice. (Table 14 ~~Table N~~, Groups 2 and 5-9). One group of mice (Table 14 ~~Table N~~, Group 1) was injected with PBS alone (control). ~~[273.]~~[[273.] Beginning 14 ~~Beginning 19~~ days post KG-1 injection mice were treated with: CONY1, Doxorubicin, CONY1-Doxorubicin conjugate, or MYLOTARG® ~~Mylotarg®~~. (MYLOTARG® ~~Mylotarg®~~ is a monoclonal antibody (anti CD33) conjugated chemically to calcheamicin recently approved by the FDA for treatment of AML patients age 60 and over in a first relapse.) Mice were treated once or three times per week for three weeks. One group (group 2) of KG-1 inoculated mice were left untreated. (Table 14). Two other groups of mice (groups 3 and 4) were injected with KG-1 cells that were previously incubated with CONY1 or 181-scFv (a negative, non-specific control antibody) in serum free RPMI containing 1% BSA at 4EC for 1 h. The antibodies were used at a concentration of 0.25mg scFv/10^8 cells (75 μg/mouse). Before injection into the mice the preincubated KG-1

cells were washed and resuspended in RPMI. The KG-1 cells in RPMI were inoculated into mice at a concentration of 75 µg scFv/ 0.2 ml RPMI per mouse. Group 3 mice were inoculated with KG-1 + CONY1, and group 4 mice were inoculated with KG-1 + 181-scFv. (Table 14). This treatment (group 3 and 4) was carried out one day after the inoculation of groups 1-2 and 5-9, *i.e.*, at five days after CYTOXAN® ~~CYTOXAN~~ injection.

Table 14

# of Mice	Group #	Inoculation	Treatment
9	1	PBS	--
11	2	KG-1	--
9	3	KG-1 + Y1	--
9	4	KG-1 + 181	--
8	5	KG-1	75 µg/mouse (2.5 mg/kg) CONY1, 3 times per week
9	6	KG-1	0.1 mg/kg Doxorubicin, 3 times per week
10	7	KG-1	5 mg/kg Doxorubicin, 1 time per week
11	8	KG-1	75 µg/mouse (2.5 mg/kg) CONY1-Doxorubicin, 3 times per week
9	9	KG-1	0.2 mg/kg MYLOTARG® ~~Mylotarg®~~ 1 time per week

At paragraph 275 please replace the original paragraph with the following paragraph:

[275.] The results are depicted in (FIGS. 36 and 37) ~~(FIGS. Tab 6, pages 5 and 6)~~. Nine out of 10 KG-1 cells-injected mice that were treated with 5mg/kg free Doxorubicin (group 7) died within three weeks after treatment initiation.

At paragraph 277 please replace the original paragraph with the following paragraph:

[277.] Overall, nearly all KG-1 injected mice developed leukemia, with average of 30% KG-1 cells in the bone marrow (as determined by FACS analysis). In general, KG-1 engraftment was confined to the bone marrow. Less than 10% KG-1 cells were found in the blood. In one case a solid tumor was observed on peritoneal wall.

At paragraph 280 please replace the original paragraph with the following paragraph:

[280.] Mice injected with KG-1 cells pre-incubated *in vitro* with CONY1 or 181-

scFv (groups 3 and 4, respectively) had a significantly lower percentage of KG-1 cells in their bone marrow.

At paragraph 281 please replace the original paragraph with the following paragraph:

[281.] The bone marrow of both mice injected with PBS only (negative control) and mice injected with KG-1 cells and treated with MYLOTARG® ~~Mylotarg™~~ (group 9) was free of KG-1 cells. These results demonstrate that this *in vivo* model is a useful model for AML.

At paragraph 282 please replace the original paragraph with the following paragraph:

[282.] The overall percentage of KG-1 cells found in the blood stream of the various groups was very low overall, with high variation within the groups. It should be noted that one mouse treated with MYLOTARG® ~~Mylotarg™~~ demonstrated relatively high percentage of KG-1 cells in the blood, but not in bone marrow.

At paragraph 284 please replace the original paragraph with the following paragraph:

[284.] On the first day of analysis, there was a significant difference between mice injected with KG-1 alone (group 2), which had higher percentage of KG-1 cells in their bone marrow, as compared to mice treated with CONY1-Doxorubicin (group 8). On the third day of analysis this situation was reversed: mice from group 8 had a higher percentage of KG-1 cells in their bone marrow when compared to mice from group 2. This situation may have resulted from the following: A) choosing mice in worse physical condition in the first day, B) proliferation of KG-1 cells in mice from group 8 during the days after treatment termination, and C) the number of mice in each group was too small to generate statistically significant results.

Pharmacokinetics of CONY1 in Mice

At paragraph 301 please replace the original paragraph with the following paragraph:

[301.] Likewise, it is within the ability of the skilled worker using the guidance

provided herein to alter the binding characteristics of an antibody, fragment, or construct to obtain a molecule with more desirable characteristics. For example, once an antibody having a desirable property ~~properties~~ is identified, random or directed mutagenesis may be used to generate variants of the antibody, and those variants may be screened for desirable characteristics.

At paragraph 302 please replace the original paragraph with the following paragraph:

[302.] Antibodies and fragments according to the present invention may also have a tag may be inserted or attached thereto to aid in the preparation and identification thereof, and in diagnostics. The tag can later be removed from the molecule. Examples of useful tags include: AU1, AU5, BTag, c-myc, FLAG, Glu-Glu ~~Glu~~, HA, His6 (SEQ ID NO: 245), HSV, HTTPHH (SEQ ID NO: 246), IRS, KT3, Protein C, S-TAG® ~~S-Tag®~~, T7, V5, and VSV-G (Jarvik and Telmer, *Ann. Rev. Gen.,* 32, 601-618 (1998)). The tag is preferably c-myc or KAK.

At paragraph 308 please replace the original paragraph with the following paragraph:

[308] In this system, the phage library (as described herein above) was designed to display scFvs, which can fold into the monovalent form of the Fv region of an antibody. Further, and also discussed herein above, the construct is suitable for bacterial expression. The genetically engineered scFvs comprise heavy chain and light chain variable regions joined by a contiguously encoded 15 amino acid flexible peptide spacer. The preferred spacer is $(Gly_4Ser)_3$ (SEQ ID NO: 247). The length of this spacer, along with its amino acid constituents provides for a nonbulky spacer, which allows the V_H and the V_L regions to fold into a functional Fv domain that provides effective binding to its target.

At paragraph 312 please replace the original paragraph with the following paragraph:

[312.] The Y1-cys-KAK ~~kak~~ was produced in a λ-pL vector in bacteria. Expression in the λ-pL vector was induced by increasing the temperature to 42°C. Inclusion bodies were obtained from induced cultures and semi-purified by aqueous solutions, to remove unwanted

soluble proteins. The inclusion bodies were solubilized in guanidine, reduced by DTT ~~DTE~~, and refolded *in vitro* in a solution based on arginine/oxidized-glutathione ~~ox-glutathione~~. After refolding, the protein was dialyzed and concentrated by tangential flow filtration to a buffer containing urea [Urea]/phosphate buffer. The protein was repurified and concentrated by ionic-chromatography in an SP-column.

At paragraph 318 please replace the original paragraph with the following paragraph:

[318] Varying the length of the spacers is yet another preferred method of forming dimers, trimers, and triamers (often referred to in the art as diabodies, triabodies and tetrabodies, respectively). Dimers are formed under conditions where the spacer joining the two variable chains of a scFv is shortened to generally 5-12 amino acid residues. This shortened spacer prevents the two variable chains from the same molecule from folding into a functional Fv domain. Instead, the domains are forced to pair with complimentary domains of another molecule to create two binding domains. In a preferred method, a spacer of only 5 amino acids (Gly_4Ser) (SEQ ID NO: 248) was used for diabody construction. This dimer can be formed from two identical scFvs, or from two different populations of scFvs and retain the selective and/or specific enhanced binding activity of the parent scFv(s), and/ or show increased binding strength or affinity.

At paragraph 330 please replace the original paragraph with the following paragraph:

[330.] More specific examples of linker compounds useful according to the present invention, include:

a. Dicarboxylic acids such as succinic acid, glutaric acid, and adipic acid;

b. Maleimido hydrazides such as N-[ε-maleimidocaproic acid] hydrazide ~~N-[□-maleimidocaproic acid] hydrazide~~] 4-[N-maleimidomethyl]cyclohexan-1-carboxylhydrazide, and N-[κ-maleimidoundecanoic acid] hydrazide ~~N-[□-maleimidoundecanoic acid] hydrazide~~;

c. PDPH linkers such as (3-[2-pyridyldithio]propionyl hydrazide) conjugated to sulfurhydryl reactive protein; and

d. Carboxylic acid hydrazides selected from 2-5 carbon atoms.

At paragraph 331 please replace the original paragraph with the following paragraph:

[331.] Linking via direct coupling using small peptide linkers is also useful. For example, direct coupling between the free sugar of, for example, the anti-cancer drug doxorubicin and a scFv may be accomplished using small peptides. Examples of small peptides include AU1, AU5, BTag, c-myc, FLAG, Glu-Glu, HA, His6 (SEQ ID NO: 245), HSV, HTTPHH (SEQ ID NO: 246), IRS, KT3, Protein C, S- TAG® ~~S-Tag®~~, T7, V5, and VSV-G.

At paragraph 341 please replace the original paragraph with the following paragraph:

[341.] Other exemplary pharmaceutical agents include doxorubicin (adriamycin), morpholinodoxorubicin, methoxymorpholinyldoxorubicin [doxorubicin, methoxymorpholinyldoxorubicin (morpholinodoxorubicin), adriamycin], cis-platinum, taxol, calicheamicin, vincristine, cytarabine (Ara-C), cyclophosphamide, prednisone, daunorubicin, morpholinodaunorubicin, methoxymorpholinyldaunorubicin, idarubicin, fludarabine, chlorambucil, interferon alpha, hydroxyurea, temozolomide, thalidomide and bleomycin, and derivatives and combinations thereof.

At paragraph 350 please replace the original paragraph with the following paragraph:

[350.] Non-limiting examples of anti-cancer or anti-leukemia pharmaceutical agents include doxorubicin (adriamycin), morpholinodoxorubicin, methoxymorpholinyldoxorubicin, ~~doxorubicin, adriamycin~~, cis-platinum, taxol, calicheamicin, vincristine, cytarabine (Ara-C), cyclophosphamide, prednisone, daunorubicin, morpholinodaunorubicin, methoxymorpholinyldaunorubicin, idarubicin, fludarabine, chlorambucil, interferon alpha, hydroxyurea, temozolomide, thalidomide and bleomycin, and derivatives thereof, an combinations thereof.

At paragraph 368 please replace the original paragraph with the following paragraph:

[368] **A leader sequence compatible for a mammalian expression system**: An exchangeable system was designed to allow convenient insertion of elements required for a full IgG molecule. The following complimentary double stranded oligonucleotides encoding

a putative leader sequence were synthesized, annealed, and ligated into the *Xho*I site of the pBJ-2 mammalian expression vector (under the SRα5 promoter). (SEQ ID NO: 249)

5'-TCGACCTCATCACCATGGCCTGGGCTCTGCTGCTCCTCACCCTCCTCACTCAGG ACACAGGGTCCTGGGCCGAT

and (SEQ ID NO: 250)

5'-GATCGATTGCACCAGCTGGATATCGGCCCAGGACCCTGTGTCCTGAGTGAGGA GGGTGAGGAGCAGCAGAGCCCAGGCCATGGTGATGAGG. Upstream of the initiation ATG codon, two Kozak elements were included. In addition, an internal *Eco*RV site was introduced between the putative cleavage site of the leader sequence and the *Xho*I site to allow subcloning of the variable regions. This modified vector was designated pBJ-3.

At paragraph 370 please replace the original paragraph with the following paragraph:

[370] 5'-TTTGATATCCAGCTGGTGGAGTCTGGGGGA (sense) (SEQ ID NO: 251) and 5'-GCTGACCTAGGACGGTCAGCTTGGT (anti-sense) (SEQ ID NO: 252) were used for the V_L PCR reaction. The cDNA product of the expected size of ~350 bp was purified, sequenced and digested with *Eco*RV and *Avr*II restriction enzymes. The same procedure was employed to amplify and purify the V_H cDNA region, using the sense and the anti-sense oligonucleotides (SEQ ID NOS: 253-254)

5'-GGGATATCCAGCTG(C/G)(A/T)GGAGTCGGGC

and

5'-GGACTCGAGACGGTGACCAGGGTACCTTG, respectively.

At paragraph 372 please replace the original paragraph with the following paragraph:

[372] For the constant CL-λ3 region, RT-PCR was performed on mRNA extracted from a pool of normal peripheral B-cells (CD19+ cells) in combination with the sense 5'-

CCGTCCTAGGTCAGCCCAAGGCTGC (SEQ ID NO: 255) and the anti-sense 5'-TTTGCGGCCGCTCATGAACATTCTGTAGGGGCCACTGT (SEQ ID NO: 256) oligonucleotides. The PCR product of the expected size (~400 bp) was purified, sequenced, and digested with *Avr*II and *Not*I restriction enzymes.

At paragraph 373 please replace the original paragraph with the following paragraph:

[373] For the constant IgG1 regions (γ chain), a human B cell clone (CMV - clone #40), immortalized at BTG, was selected for PCR amplification. This clone was shown to secrete IgG1 against human CMV and was also shown to induce ADCC response in *in-vitro* assays. For the CH1-CH3 cDNA, oligonucleotides (SEQ ID NOS: 257-258)

5'-ACCGCTCGAGTGC(T/C)TCCACCAAGGGCCCATC(G/C)GTCTTC (sense)

and

5'-TTTGCGGCCGCTCATTTACCC(A/G)GAGACAGGGAGAGGCT (anti-sense) were synthesized and used for PCR amplification. As described for the CL cDNA encoding sequence, the PCR product of expected size (~1500 bp) was purified, sequenced, and digested with *Avr*II and *Not*I restriction enzymes.

At paragraph 386 please replace the original paragraph with the following paragraph:

[386.] **Binding of full size IgG-Y1 molecule:** Binding experiments were performed to determine the level of binding of the IgG-Y1 molecule compared to the binding level of the scFv-Y1 molecule. A two-step staining procedure was employed, wherein 5 ng of IgG-Y1 were reacted with both RAJI cells (negative control, FIGs. 44-47a ~~Figure 44~~) and Jurkat cells (Y1 positive cells, FIGs. 44-47b and 44-47c ~~Figure 44~~). For detection, PE-labeled goat anti-human IgG was used (FIGs. 44-47c). Similarly, 1 μg of scFv-Y1 was reacted with Jurkat cells (FIGs. 44-47b), and PE-labeled rabbit anti-scFv was used for detection. Results indicate that both IgG-Y1 and scFv-Y1 bind to Jurkat cells, with approximately 10^3-fold more scFv-Y1 molecules needed to obtain a level of detection similar to that of the IgG-Y1.

Example 6: Preparation of Fab and F(ab')$_2$ fragments derived from the full IgG Y1 antibody.

At paragraph 425 please replace the original paragraph with the following paragraph:

[425] The vector pHEN-Y1, encoding the original Y1, was amplified using PCR for both the V_L and the V_H regions, individually. The sense oligonucleotide 5'- AACTCGAGTGAGCTGACACAGGACCCT (SEQ ID NO: 259), and the anti-sense oligonucleotide 5'-TTTGTCGACTCATTTCTTTTTTGCGGCCGCACC (SEQ ID NO: 260) were used for the V_L PCR reaction. The cDNA product of the expected size of ~350 bp was purified, sequenced, and digested with *Xho*I and *Not*I restriction enzymes.

At paragraph 426 please replace the original paragraph with the following paragraph:

[426] The same procedure was employed to amplify the V_H region (using the sense oligonucleotide 5'-ATGAAATACCTATTGCCTACGG (SEQ ID NO: 261) and anti-sense oligonucleotide 5'-AACTCGAGACGGTGACCAGGGTACC) (SEQ ID NO: 262). The V_H PCR product was digested with *Nco*I and *Xho*I restriction enzymes. A triple ligation procedure into the pHEN vector, pre-digested with *Nco*I-*Not*I, was employed. The final vector was designated pTria-Y1.

At paragraph 428 please replace the original paragraph with the following paragraph:

[428] The pTria-Y1 vector from above was linearized with *Xho*I restriction enzyme, and synthetic complimentary double stranded oligonucleotides (5'-TCGAGAGGTGGAGGCGGT (SEQ ID NO: 263) and 5' TCGAACCGCCTCCACCTC) (SEQ ID NO: 264) were pre-annealed and ligated into the *Xho*I site, between the Y1-heavy and Y1-light chains. This new vector was designated pDia-Y1. As described for the triabodies, the DNA sequence and protein expression was confirmed.

At paragraph 431 please replace the original paragraph with the following paragraph:

[431.] The binding of Y1-scFv was compared to that of diabodies and triabodies. In this analysis ~~Figure 44~~, the binding profile of all three forms was very similar, indicating that

the above modifications in the molecule did not alter, conceal or destroy the apparent binding affinity of Y1 to its ligand.

EXAMPLE 12: A Study of the Affinity of the S-S Y1-Dimer in Comparison to CONY1 and Y1-IgG, using a Radioreceptor Binding Assay with KG-1 Cells

At paragraph 434 please replace the original paragraph with the following paragraph:

[434.] In a second RRA using labeled CONY1, a 100 ng/tube of ^{125}I-Y1-IgG was used, and competition was performed with each of the three molecules. The results are provided in Figure 47. This figure shows that the affinity of the S-S dimer was 20 times higher than that of CONY1. A rough estimate of the affinity of CONY 1 in this experiment is 10^{-6}M. The corresponding affinity of the dimer is, therefore, 5x 10^{-8} M.

EXAMPLE 13: Production of Y1-cys-KAK ~~kak~~ (cysteine dimer)

At paragraph 435 please replace the original paragraph with the following paragraph:

[435.] One liter of λpL-y1-cys-KAK ~~kak~~ bacterial culture was induced at 42°C for 2-3 hrs. This culture was centrifuged at 5000 RPM for 30 minutes. The pellet was resuspended in 180 ml of TE (50mM Tris-HCl pH 7.4, 20mM EDTA). 8 ml of lysozyme (from a 5 mg/ml stock) was added and incubated for 1 hr. 20 ml of 5M NaCl and 25 ml of 25% Triton was added and incubated for another hour. This mixture was centrifuged at 13000 RPM for 60 minutes at 4° C. The supernatant was discarded. The pellet was resuspended in TE with the aid of a tissuemiser (or homogenizer). This process was repeated 3-4 times until the inclusion bodies (pellet) were gray/light brown in color. The inclusion bodies were solubilized in 6M Guanidine-HCl, 0.1M Tris pH 7.4, 2 mM EDTA (1.5 grams of inclusion bodies in 10 ml solubilization buffer provided ~10 mg/ml soluble protein). This was incubated for at least 4 hrs. The protein concentration was measured and brought to a concentration of 10 mg/ml. DTT ~~DTE~~ was added to a final concentration of 65 mM and incubated overnight at room temperature. Re-folding was initiated by dilution of 10 ml of

protein (drop by drop) to a solution containing 0.5 M Arginine, 0.1 M Tris pH 8, 2 mM EDTA, 0.9 mM GSSG. The re-folding solution was incubated at ~10° C for 48 hrs. The re-folding solution containing the protein was dialyzed in a buffer containing 25 mM Phosphate buffer pH 6, 100 mM Urea, and concentrated to 500 ml. The concentrated/dialyzed solution was bound to an SP-sepharose column, and the protein was eluted by a gradient of NaCl (up to 1M).

EXAMPLE 14: ELISA to GC (glycocalicin)

At paragraph 436 please replace the original paragraph with the following paragraph:

[436.] 100 ml of purified glycocalicin was incubated in a 96 flat well MaxiSorp™ ~~maxisorp~~ plates, overnight at 4 degrees celsius. The plate was washed with PBST (PBS+0.05% Tween ~~tween~~) 3 times, then 200 ml of PBST-milk (PBST + 2% Non fat milk), for 1 hr at room temperature. The plate was washed with PBST, and the monomer or dimer (100 ml) was added in PBST-milk at different concentrations for 1hr at room temp. Then the plate was washed and anti-V_L polyclonal (derived from immunized rabbits with V_L derived from Y1) (1:100 diluted in PBST-milk) was added for an hour. The plate was washed and anti-rabbit HRP was added for an additional hour. The plate was washed 5 times and 100 µl TMB substrate was added for approximately 15 minutes then 100 µl of 0.5 H_2SO_4 was added to stop the reaction. The optical density of the plate was measured at 450nm in an ELISA reader.

EXAMPLE 15: *E. coli* Expression of Recombinant Glycocalicin (GC)

At paragraph 439 please replace the original paragraph with the following paragraph:

[439.] A construct was designed where the following sequence, LNDIFEAQKIEWHE (SEQ ID NO:268), was added at the C-terminus of the Y1 by PCR and cloning into an IPTG inducible expression vector cassette. The clone was named Y1-biotag. This sequence is a substrate for the enzyme BirA, that in the presence of free biotin, the enzyme is capable of covalently connecting biotin to the lysine (K) residue (Phenotypic

analysis of antigen-specific T lymphocytes. Science. 1996 Oct 4;274(5284):94-6, Altman JD et al). This construct was produced as inclusion bodies in BL21 bacterial cells. Refolding was performed as described previously. Inclusion bodies were solubilized in guanidine-DTT ~~guanidine-DTE~~. Refolding was done by dilution in a buffer containing arginine-Tris-EDTA ~~arginine-tris-EDTA~~. Dialysis and concentration was performed followed by HiTrapQ ionic exchange purification.